THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

How Do We Treat MDS in 2024?

Omer Jamy, MD

Disclosures

- Advisory board participation: Ascentage, MaaT, TERN, Sobi

Risk Stratification

International Prognostic Scoring System = IPSS
Revised IPSS = R-IPSS
Molecular IPSS = M-IPSS

IPSS-M

Bernard et al. NEJM Evidence 2021

Input:

- **Clinical variables:** age, sex, Hb, PLT, BM blasts%, IPSS-R cytogenetic risk.
- **Molecular variables:** 31 gene panel

  (17 genetic variables from 16 main effect genes: *TP53* allelic status, *SF3B1*^{5q}, *SF3B1*$^{\alpha}$, *SF3B1*$^{\beta}$. Number of additional mutations in *BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2,* and *WT1*

  &

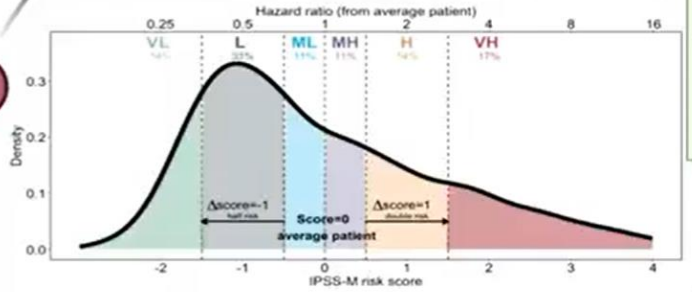
  1 genetic variable from 15 residual genes: *ASXL1, CBL, DNMT3A, ETV6, EZH2, FLT3, IDH2, KRAS, MLL-PTD, NPM1, NRAS, RUNX1, SRSF2,* and *U2AF1)*

2

3

Output: six risk strata

Very Low | Low | Moderate Low | Moderate High | High | Very High



Online calculator:

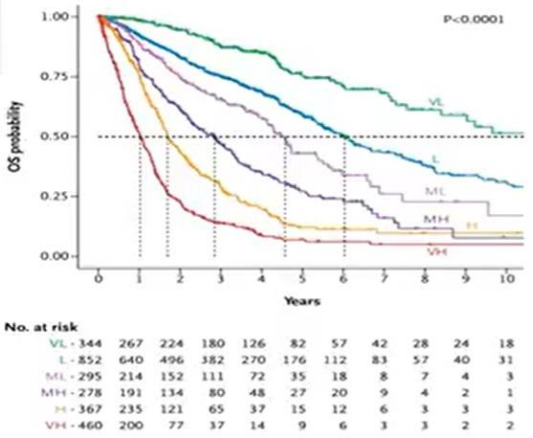
https://mds-risk-model.com/

1

Pt with MDS

4 **Information sharing with the patients**

Risk Score	VL	Low	ML	MH	H	VH
Median LFS, yrs	9.7	5.9	4.5	2.3	1.5	0.76
Median OS, yrs	10.6	6	4.6	2.8	1.7	1.0
AML transformation by 1yr, %	0	1.7	4.9	9.5	14.3	28.2



No. at risk

VL	344	267	224	180	126	82	57	42	28	24	18
L	852	640	496	382	270	176	112	83	57	40	31
ML	295	214	152	111	72	35	18	8	7	4	3
MH	278	191	134	80	48	27	20	9	4	2	1
H	367	235	121	65	37	15	12	6	3	3	3
VH	460	200	77	37	14	9	6	3	3	2	2

Input:

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2

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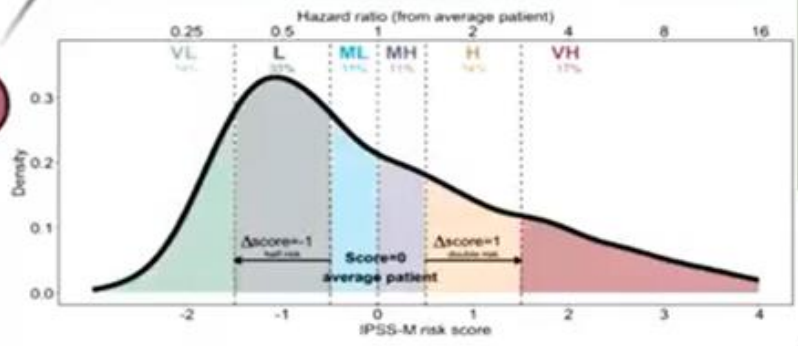
Output: six risk strata

Very Low | Low | Moderate Low |
Moderate High | High | Very High



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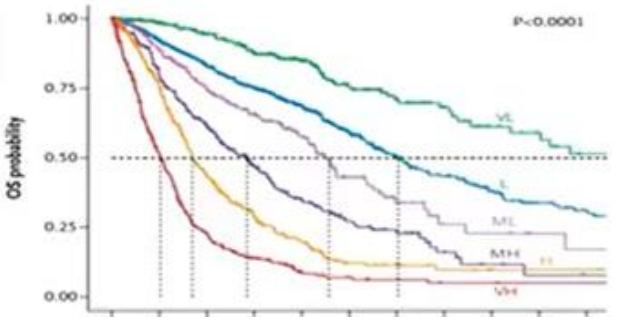
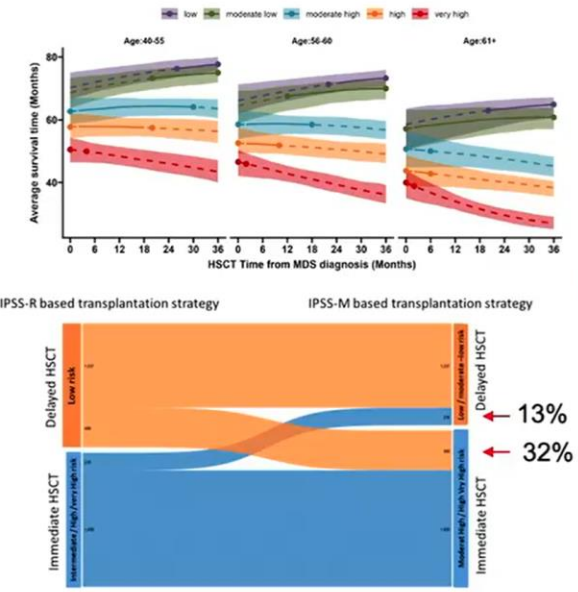


IPSS-M Provides Best Guidance

62 yo asymptomatic male	
Hb	10.5 gm/dl
WBC	3.0 k / microL
ANC	0.8 k /microL
Platelet	90 k/ microL
BM	Erythroid and megakaryocytic dysplasia, Myeloblasts-4%
KT	46, XY [20]
NGS	Two ***TP53*** Mutations (max. VAF- **35%**)

IPSS-M based allo-HSCT ↑ Life expectancy



How should we treat?

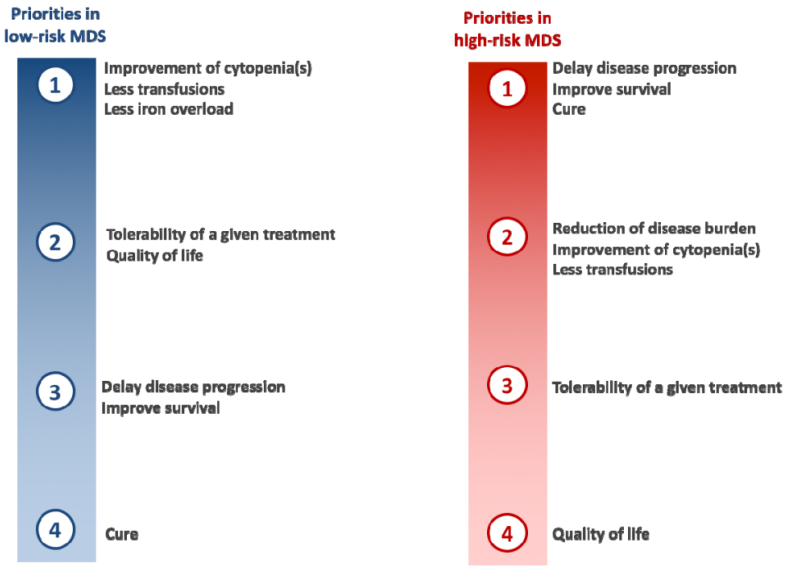
- Start HMA now
- Start HMA when Blast >5%
- Send for allo-HSCT now
- Send for transplant later directly
- Send for transplant later after HMA

Tentori CA,…,Ball S, et al. JCO 2024

Risk

- Lower-risk MDS = Very low, low, moderate-low
- Higher-risk MDS = moderate-high, high, very high

Goal

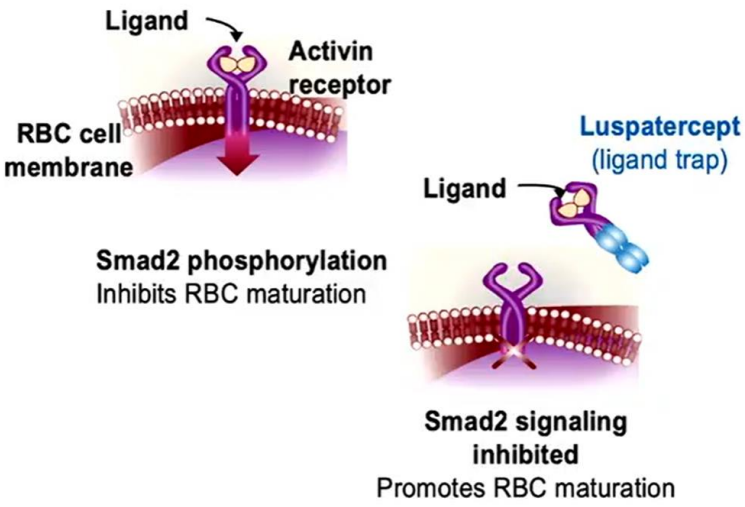

Priorities in low-risk MDS
1
Improvement of cytopenia(s)
Less transfusions
Less iron overload
2
Tolerability of a given treatment
Quality of life
3
Delay disease progression
Improve survival
4
Cure
Priorities in high-risk MDS
1
Delay disease progression
Improve survival
Cure
2
Reduction of disease burden
Improvement of cytopenia(s)
Less transfusions
3
Tolerability of a given treatment
4
Quality of life

Low-risk MDS: Do we need to treat?

- Not all patients need treatment
- Therapies don’t make you live longer
- Focus on quality of life (low blood counts causing problems)

"*COMMANDS*" for Frontline Luspatercept

Phase 3 RCT: Luspa vs. ESA in New LR-MDS w Transfusion-dependent Anemia



Primary Endpoint: RBC-TI for at least 12 weeks + mean Hb increase of 1.5 gm/dl (week 1-24)

Key eligibility criteria

- ≥ 18 years of age
- IPSS-R very low-, low, or intermediate-risk MDS (with or without RS) by WHO 2016, with < 5% blasts in bone marrow[a]
- Required RBC transfusions (2-6 pRBC units/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO < 500 U/L
- ESA-naive

Patients stratified by:

- Baseline sEPO level
- Baseline RBC transfusion burden
- RS status

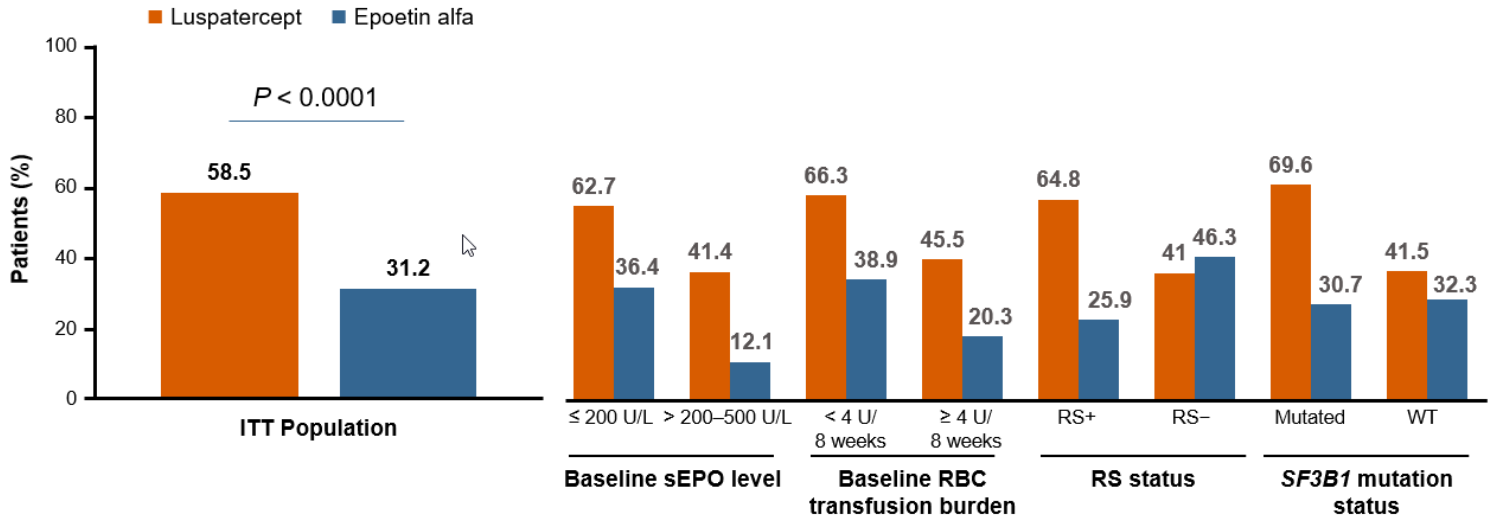
Randomized 1:1

- **Luspatercept (N = 178)** 1.0 mg/kg s.c. Q3W titration up to 1.75 mg/kg
- **Epoetin alfa (N = 178)[b]** 450 IU/kg s.c. QW titration up to 1050 IU/kg

Della Porta et al. EHA, 2023

COMMANDS Trial
Achievement of Primary Endpoint in Different Patient Subgroups

Primary endpoint: RBC-TI ≥ 12 weeks with concurrent mean Hb increase ≥ 1.5 g/dL (weeks 1–24)



RS status, baseline sEPO level, and baseline RBC transfusion burden were prespecified factors for randomization. *SF3B1* mutation status was a post hoc subgroup analysis. WT, wild type.

Guillermo Garcia-Manero, et al. Presented at ASCO 2023: Abstract 7003.

- Luspatercept has a manageable and predictable safety profile, consistent with previous clinical experience

Patients, n (%)	Luspatercept (n = 178)		Epoetin alfa (n = 176)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Heme-related TEAEs				
Anemia	17 (9.6)	13 (7.3)	17 (9.7)	12 (6.8)
Thrombocytopenia	11 (6.2)	7 (3.9)	3 (1.7)	1 (0.6)
Neutropenia	9 (5.1)	7 (3.9)	13 (7.4)	10 (5.7)
Leukocytopenia	2 (1.1)	0	3 (1.7)	0
TEAEs of interest				
Fatigue	26 (14.6)	1 (0.6)	12 (6.8)	1 (0.6)
Diarrhea	26 (14.6)	2 (1.1)	20 (11.4)	1 (0.6)
Peripheral edema	23 (12.9)	0	12 (6.8)	0
Asthenia	22 (12.4)	0	25 (14.2)	1 (0.6)
Nausea	21 (11.8)	0	13 (7.4)	0
Dyspnea	21 (11.8)	7 (3.9)	13 (7.4)	2 (1.1)
TEE	8 (4.5)	5 (2.8)	5 (2.8)	1 (0.6)

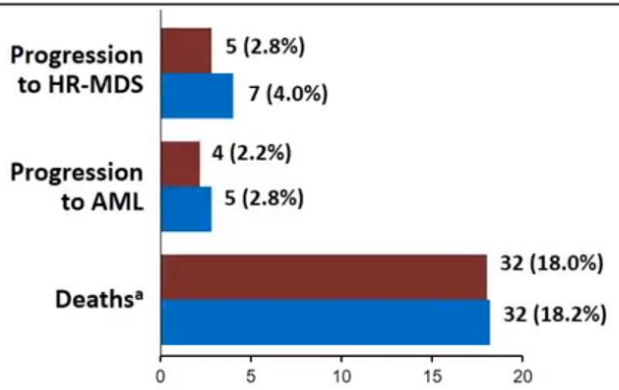
Safety data are not exposure-adjusted. [a]Deaths during treatment period and post-treatment period. TEAE, treatment-emergent adverse event; TEE, thromboembolic event.

TEAEs (any grade)

164 (92.1%) luspatercept
150 (85.2%) epoetin alfa

Median treatment duration, weeks

41.6 (range: 0–165) luspatercept
27.0 (range: 0–171) epoetin alfa



Platzbecker et al https://doi.org/10.1016/S0140-6736(23)00874-7

CONCLUSIONS

- COMMANDS study achieved its primary endpoint
- FDA approved for treatment of anemia without previous ESAs in adult patients with very low- to intermediate-risk MDS who may require regular red blood cell transfusions

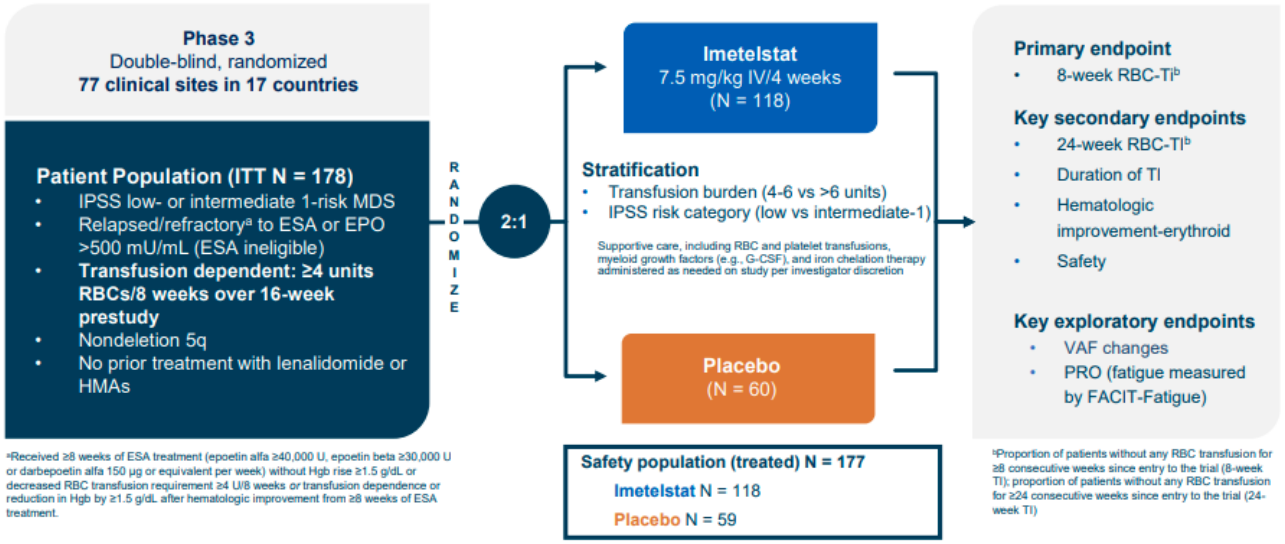
Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial

Uwe Platzbecker, Valeria Santini*, Pierre Fenaux, Mikkael A Sekeres, Michael R Savona, Yazan F Madanat, Maria Díez-Campelo, David Valcárcel, Thomas Illmer, Anna Jonášová, Petra Bělohlávková, Laurie J Sherman, Tymara Berry, Souria Dougherty, Sheetal Shah, Qi Xia, Libo Sun, Ying Wan, Fei Huang, Annat Ikin, Shyamala Navada, Faye Feller, Rami S Komrokji†, Amer M Zeidan†*

- Telomerase inhibitor
- FDA approved in Low-, intermediate 1 transfusion-dependent anemia who failed or are not candidates for ESA
- Injection once every 4 weeks

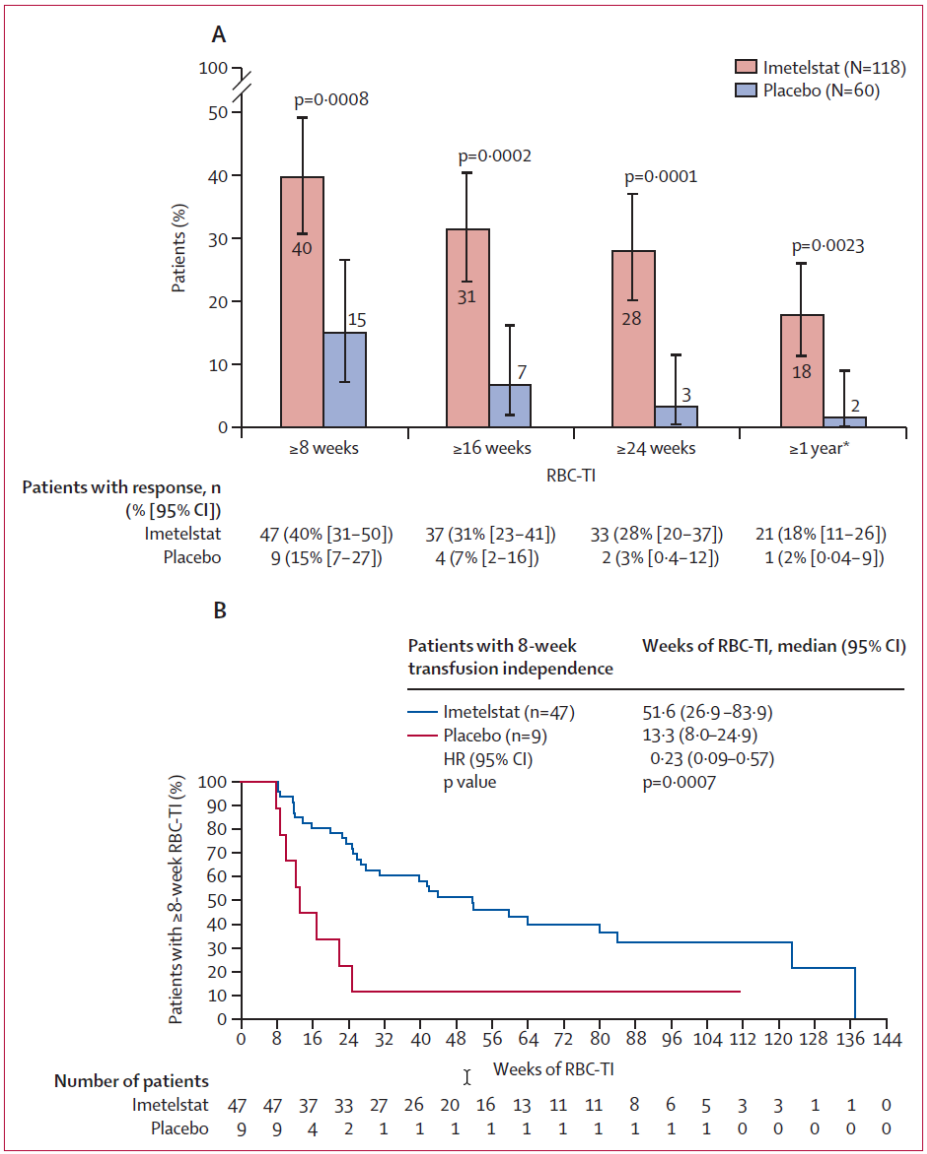
Lancet 2024; 403: 249–60 December 1, 2023 https://doi.org/10.1016/S0140-6736(23)01724-5

IMerge Phase 3 Trial: Imetelstat in Patients With LR-MDS Relapsed/Refractory to ESA or EPO[1]



[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U or darbepoetin alfa 150 µg or equivalent per week) without Hgb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U/8 weeks *or* transfusion dependence or reduction in Hgb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment.

[b]Proportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); proportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI)


A
Imetelstat (N=118)
Placebo (N=60)
Patients (%)
p=0·0008
p=0·0002
p=0·0001
p=0·0023
40
15
31
7
28
3
18
2
≥8 weeks
≥16 weeks
≥24 weeks
≥1 year*
RBC-TI
Patients with response, n (% [95% CI])
Imetelstat 47 (40% [31–50]) 37 (31% [23–41]) 33 (28% [20–37]) 21 (18% [11–26])
Placebo 9 (15% [7–27]) 4 (7% [2–16]) 2 (3% [0·4–12]) 1 (2% [0·04–9])
B
Patients with 8-week transfusion independence
Weeks of RBC-TI, median (95% CI)
Imetelstat (n=47) 51·6 (26·9–83·9)
Placebo (n=9) 13·3 (8·0–24·9)
HR (95% CI) 0·23 (0·09–0·57)
p value p=0·0007
Patients with ≥8-week RBC-TI (%)
Weeks of RBC-TI
Number of patients
Imetelstat 47 47 37 33 27 26 20 16 13 11 11 8 6 5 3 3 1 1 0
Placebo 9 9 4 2 1 1 1 1 1 1 1 1 1 1 0 0 0 0 0

Low-risk MDS – Symptomatic Anemia: Erythroid growth factors

- ESA: erythropoietin or darbepoetin (not FDA approved). Can be used if luspatercept is not available
  - Improves QoL
  - Predictive markers
    - sEPO< 100 U/L: >70% response rate to ESA
    - sEPO> 500 U/L: response rate is <10%

Low-risk MDS - Neutropenia

- Benefits of therapy less clear (no FDA approved therapies)
- GCSF improves numbers[1]
  - Never shown survival benefit
  - Never shown QoL benefit
  - Marginal improvement of incidence of infection
- Prophylactic antibiotics
  - No benefit except for recurrent infections (unless on HMA)

1. Steensma, D. P. Hematopoietic growth factors in myelodysplastic syndromes. Semin. Oncol. 38, 635–647 (2011).

Low-risk MDS - thrombocytopenia

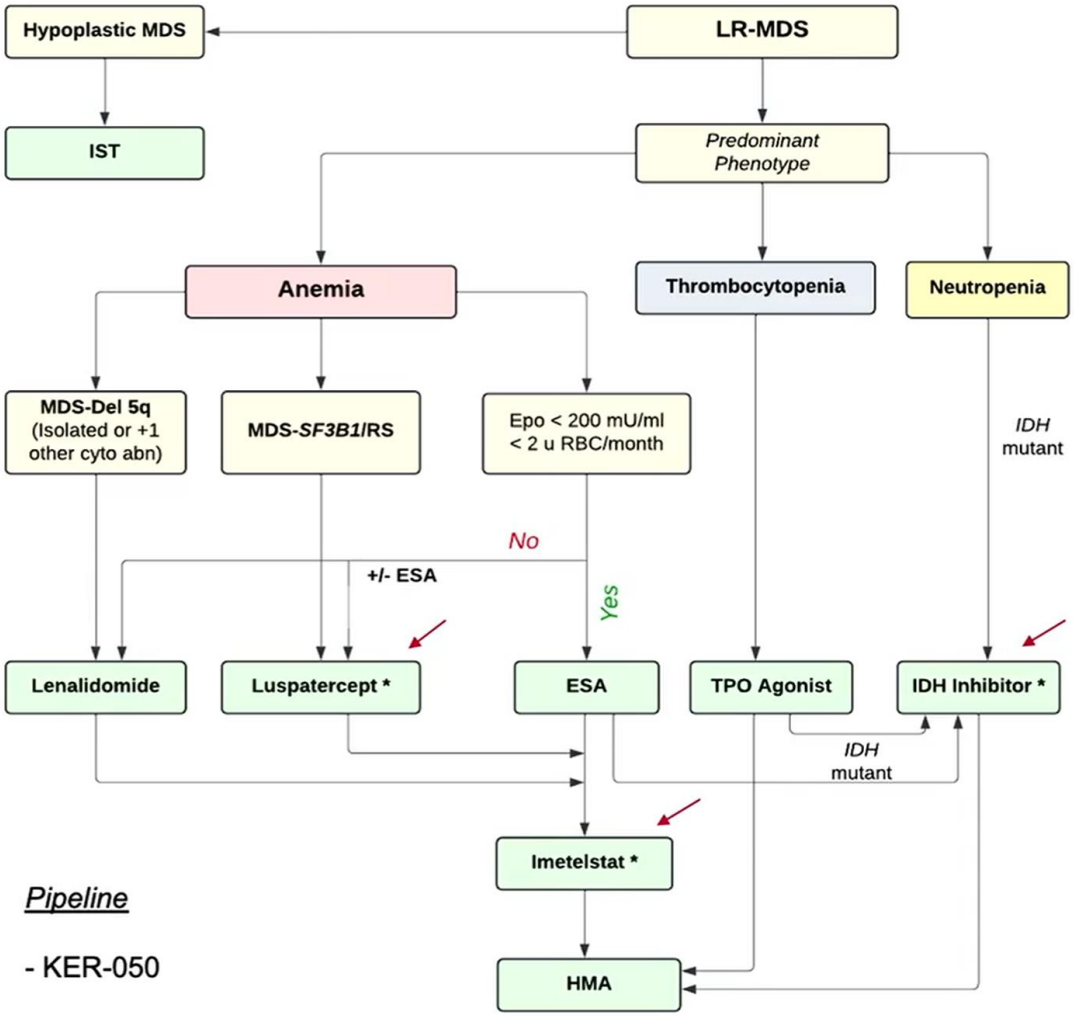
- Eltrombopag (not FDA approved)
  - can reduce transfusion
  - can reduce bleeding in severe thrombocytopenia (not FDA approved)
- No significant increase of progression to AML

1. Steensma, D. P. Hematopoietic growth factors in myelodysplastic syndromes. Semin. Oncol. 38, 635–647 (2011).

Low risk MDS - HMA

- Clinical trial after luspaterecept failure should be considered
- AZA 7-day after EPO failure: ORR was 35% [1]
- 5-day AZA is probably equivalent to 7-day AZA in ORR [2]
- First-line (EPO naïve) Decitabine 3-days: RBC-TI 32% [3]
- Decitabine-Cedazuridine (Inqovi): approved for IPSS int1, 2, high [4]
- ASTX727-LD trial. Recently finished at UAB.
  - Lower dose of Inqovi
  - Includes IPSS low and Int1

1. Thepot et al. Haematologica. 2016 Aug; 101(8): 918–925
2. Shapiro et al. BMC Hematol. 2018 Jan 31;18:3.
3. Jabbour E, Blood. 2017;130(13):1514–1522
4. Garcia-Manero. Blood (2020) 136 (6): 674–683.

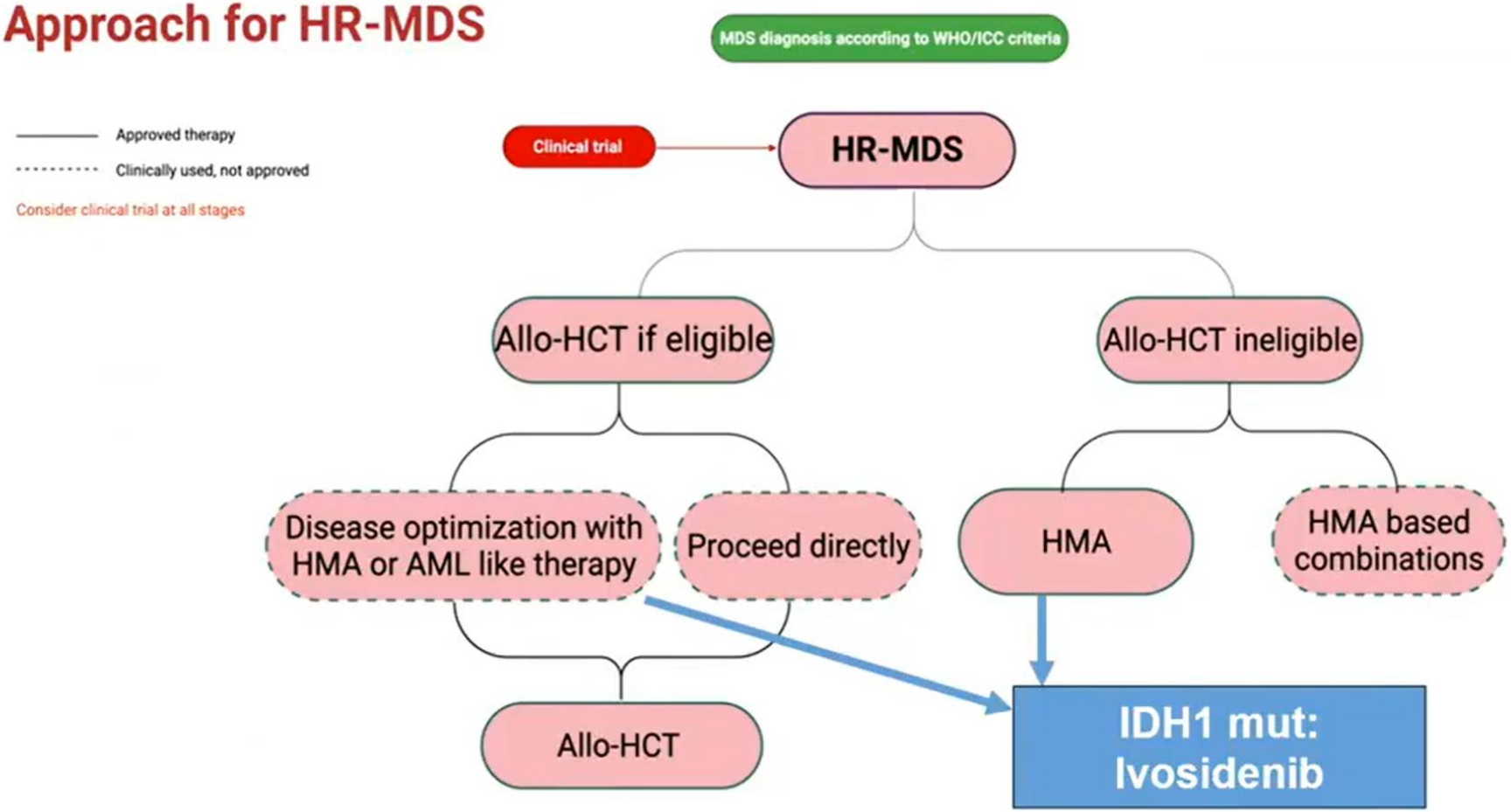


How I Treat Lower-Risk MDS in 2024

* New or upcoming approvals

Higher-risk MDS

Approach for HR-MDS

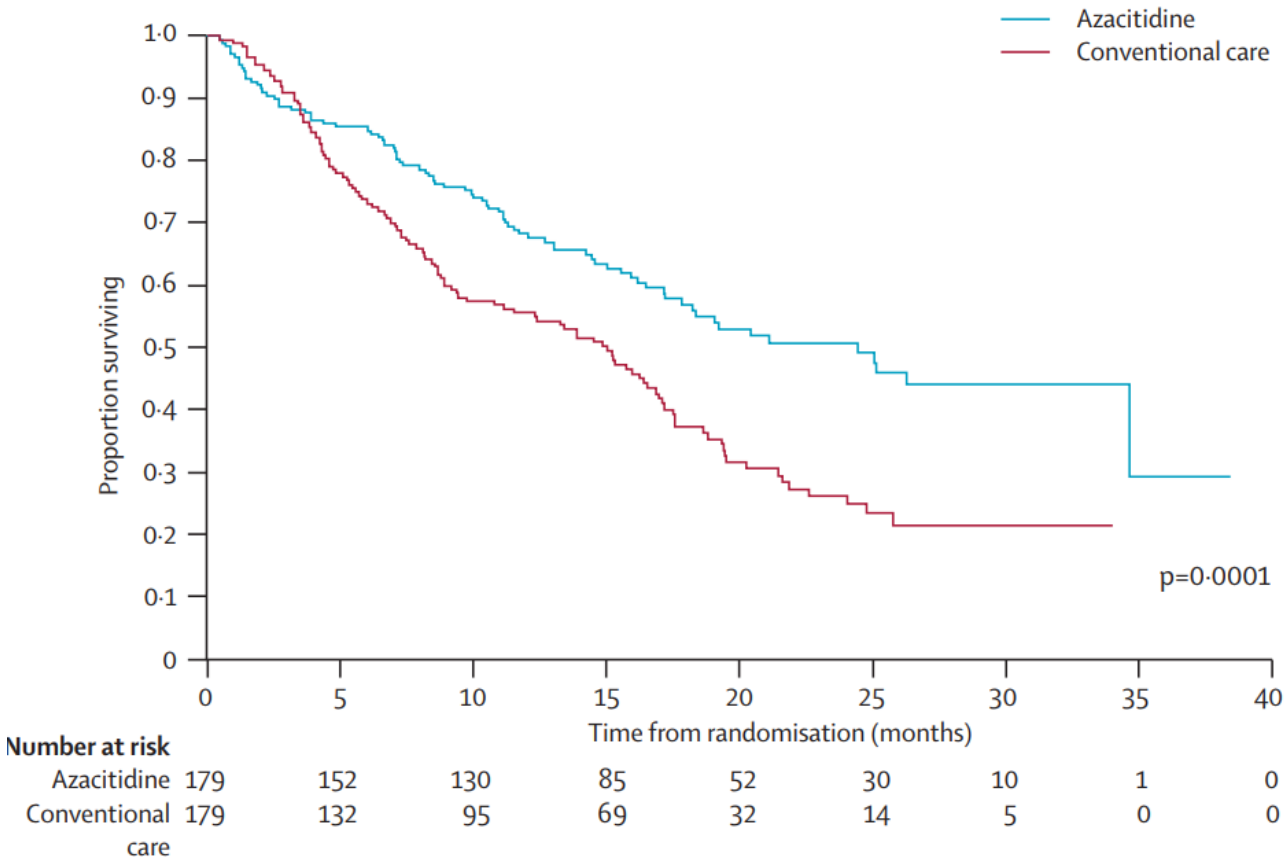


The Graveyard for HMA-based combinations: Are IWG 2006 response criteria moving agents with minimal clinical benefits to phase 3 trials?

- HMA + Lenalidomide
- HMA + Vorinostat
- HMA + volasertib
- HMA + Eltrombopag
- HMA + romiplostim
- HMA + Pracinostat
- HMA + Durvalumab
- HMA + Pevonedistat
- HMA + APR246
- HMA + Magrolimab

Last drug approved for higher risk MDS in the frontline setting was in 2006 (IV decitabine) - Aside from oral DEC/CED which was approved in 2020 based on PK equivalence to IV decitabine

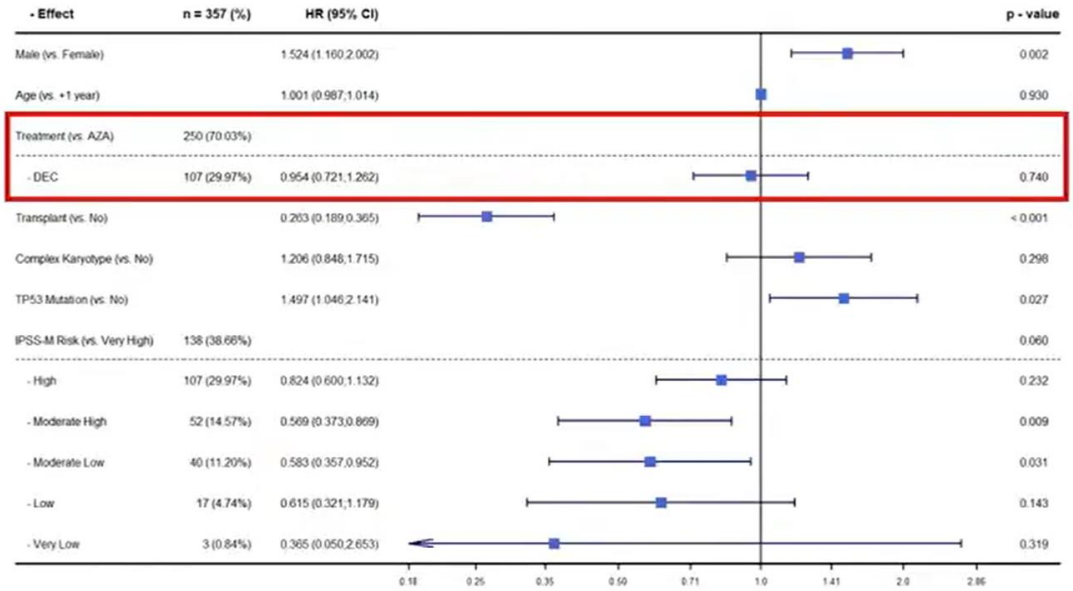
AZA-001



Fenaux, P. et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. Lancet Oncol. 2009

No difference in clinical outcomes between AZA and Dec (N=919)

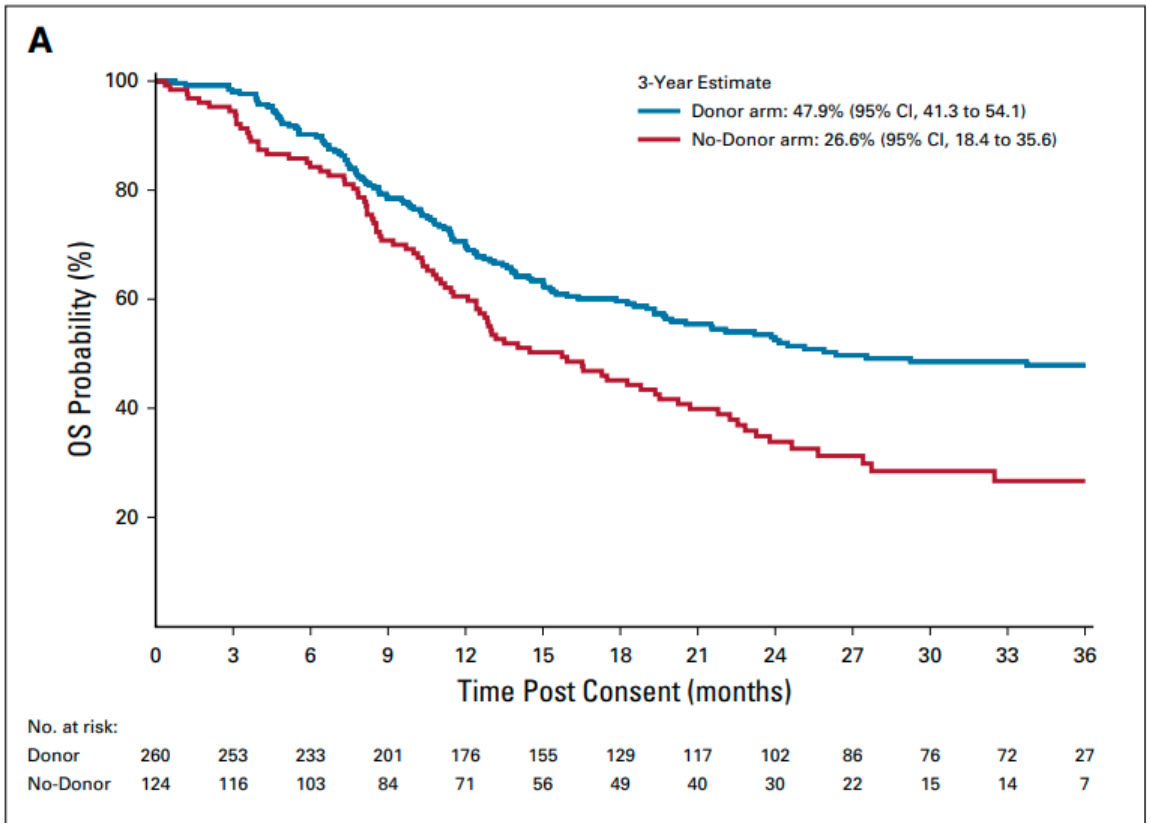
- **No difference in response rates of OS between AZA and DEC monotherapy (Hazard ratio [HR]: 0.95, 95% CI: 0.72 – 1.26; p=0.740) in adjusted analyses**
- **Other factors (e.g., *TP53* mutations, complex karyotype) are more relevant to outcomes than the type of HMA used.**



Bewersdorf J,,,,,Zeidan A. ASH 2023. Abstract 4613

MDS

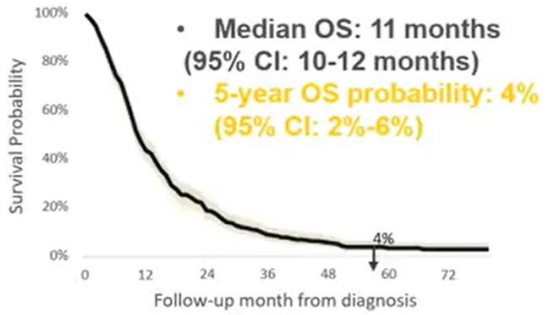
IPSS-R Risk Category	Overall Score	Median Survival (years)	25% AML Progression (years)	Transplant
Very low	≤1.5	8.8	Not reached	**No Allo HCT**
Low	>1.5 - ≤3.0	5.3	10.8	
Intermediate	>3.0 - ≤4.5	3.0	3.2	**Allo HCT if acceptable risk of TRM**
High	>4.5 - ≤6.0	1.6	1.4	**Allo HCT**
Very high	>6.0	0.8	0.7	

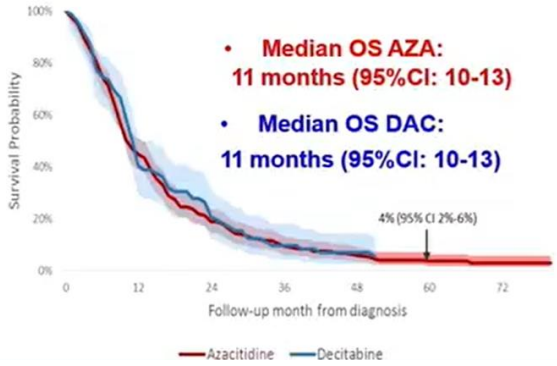

A
3-Year Estimate
Donor arm: 47.9% (95% CI, 41.3 to 54.1)
No-Donor arm: 26.6% (95% CI, 18.4 to 35.6)
OS Probability (%)
100
80
60
40
20
0
3
6
9
12
15
18
21
24
27
30
33
36
Time Post Consent (months)
No. at risk:
Donor 260 253 233 201 176 155 129 117 102 86 76 72 27
No-Donor 124 116 103 84 71 56 49 40 30 22 15 14 7

Long-term survival of MDS patients treated with HMAs who do not undergo transplantation

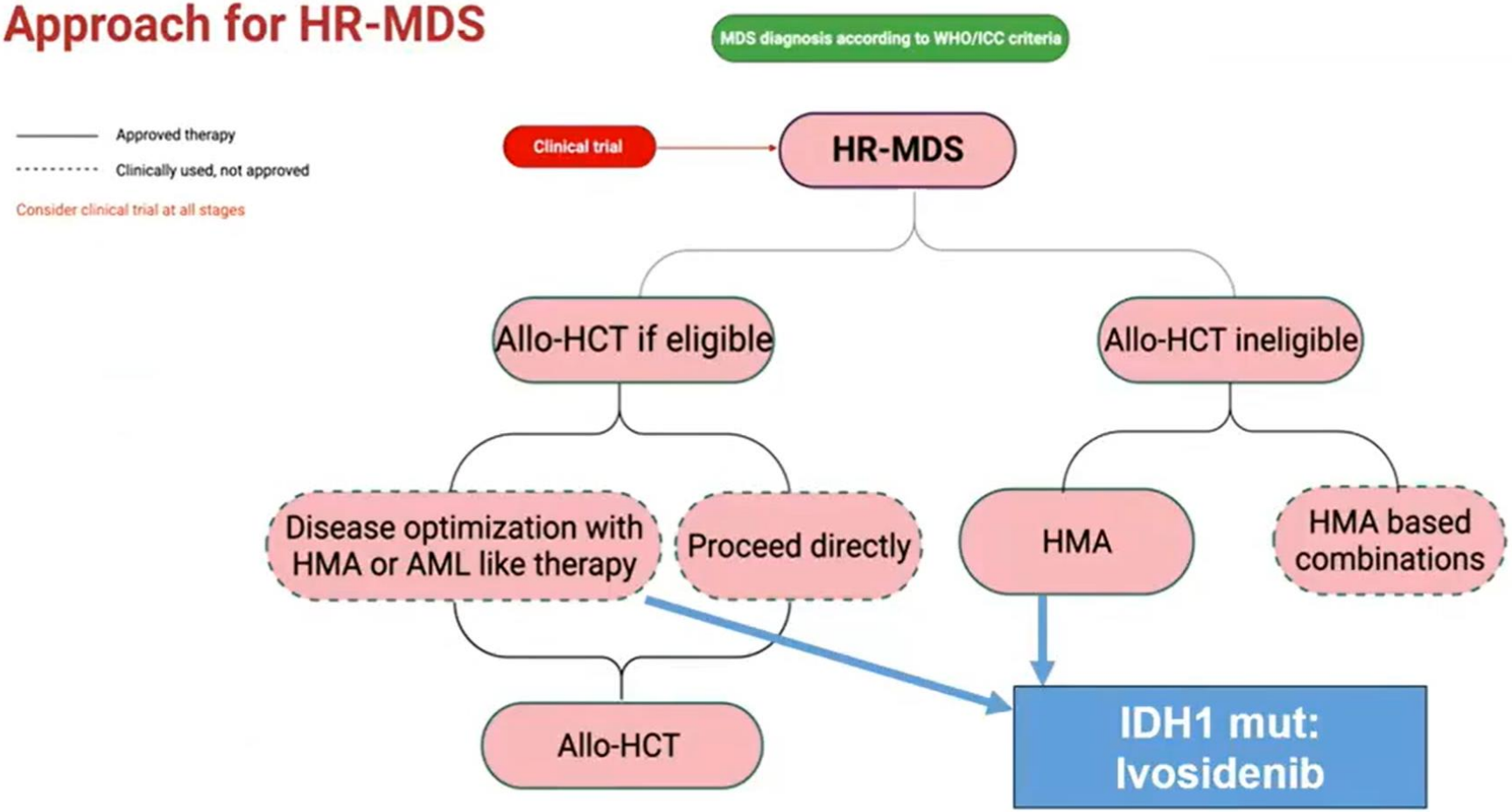
- 1187 total MDS patients
- RAEB: 336 (23.8% of all MDS patients)
- Age: 77 years (IQR 72-81)
- AZA: 79% DAC: 21%
- Median 5 cycles of HMA therapy
- ≥4 / ≥ 6 cycles of HMA therapy: 73%/ 50%
- AZA vs DAC: No difference in median HMA cycles

Even among patients who received at least 6 cycles of HMA therapy:
Five-year OS probability 6%
(95% CI: 3 -11%)





Approach for HR-MDS



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Thank you!